

Pathogenetic mechanisms of angina pectoris: expanding views*

ATTILIO MASERI†

From CNR Laboratory of Clinical Physiology, and University of Pisa, Italy

It was with pride that I accepted the honour of giving the Thomas Lewis Lecture for 1977 and I have chosen to present a subject to which we have devoted our main research efforts during the past 10 years. This Memorial Lecture seems to me an appropriate occasion to present our findings, because they represent the fruit of investigations performed in the scientific spirit of Sir Thomas and because they bring objective support to an hypothesis that he had brilliantly anticipated over 40 years ago,¹ on the basis of acute clinical observations and of logical deductions.

In the first part of my presentation I wish to outline the considerations that inspired our studies, in the second I will illustrate our results, and in the third I will put forward the implications of our expanding views on angina pectoris.

Traditional hypothesis

It is generally accepted that angina pectoris is caused by a transient, acute imbalance between myocardial demand and coronary blood supply. This imbalance is traditionally ascribed to coronary artery stenosis which sets a fixed limit to the possible increase in myocardial blood flow so that angina ensues whenever oxygen supply falls short of myocardial metabolic demand. This has been proven repeatedly to be a possible mechanism of angina pectoris, and as a result a rather restrictive definition of angina pectoris has gained acceptance. Thus, Friedberg² writes: "... the occurrence of the pain or pressure with effort is an essential element of the syndrome although it does not occur invariably with the same exertion. The pain of angina pectoris may occur at rest, but if it does not also occur with effort or cannot be reproduced by bodily exertion the diagnosis of angina pectoris may be questioned." Thus, though he recognised that angina might occur with variable levels of exertion and even at

rest: (1) he implicitly attributed the variable threshold of angina only to different levels of myocardial demand for the same work; and (2) he practically denied the existence of angina at rest with unimpaired exercise tolerance and the possible role of a functional variability of myocardial blood supply. By extrapolation, this opinion helped to generate the notion that the only variable capable of determining a transient acute imbalance between myocardial demand and supply (and thus produce myocardial ischaemia) was an excessive increase in myocardial demand relative to the fixed limitation of supply caused by coronary atherosclerosis. The conclusions of the editorial by James³ that "the most frequent explanation for angina without coronary disease is an incorrect interpretation of the coronary arteriogram" is a clear expression of a concept so deeply ingrained that it was difficult to recognise that it was actually a hidden assumption. In fact, the demonstration of stenosis of a coronary artery cannot be considered, *per se*, as proof that attacks of angina result from an increase in myocardial demand beyond supply; it is also necessary to show that they occur because local coronary flow reserve is exceeded.

Conflicting findings

Several observations contradict the traditional hypothesis that the only mechanism of angina is an excessive increase in myocardial demand in the presence of critical coronary stenosis and suggest that the relation between coronary atherosclerosis and clinical manifestation of the disease is a direct one.⁴

(1) A review of the published reports discloses that about 10 per cent of patients with angina have normal coronary arteries or no critical lesions.⁵ Furthermore, about 10 per cent of patients with "unstable angina" and typical electrocardiographic changes had to be excluded from randomised surgical trials because they were free from significant coronary stenosis.^{6 7}

(2) In patients with angina no reasonable

* Thomas Lewis Lecture, London, 24 November 1977

† Present address: Royal Postgraduate Medical School, Hammer-smith Hospital, London W12 0HS.

prediction of the extent of the coronary stenosis can be made on the basis of the severity of symptoms.⁸⁻¹⁴ Furthermore, the extent of coronary atherosclerosis in patients with unstable angina is similar to that of patients with stable angina.^{15 16}

(3) An appreciable number of subjects with documented severe coronary atherosclerosis have a normal effort electrocardiogram despite full exercise stressing.^{14 17} These reports are consistent with the findings at necropsy of severe coronary atherosclerosis in a considerable number of asymptomatic persons dying of non-cardiac causes.¹⁸⁻²⁰ Furthermore, the presence or absence of clinical symptoms cannot be related to the variable development of collaterals, these collaterals being related only to the degree of coronary stenoses.²⁰ Thus, the comparison of the high incidence of coronary atherosclerosis in the general population with the relatively low incidence of ischaemic heart disease suggests that the presence of stenoses, *per se*, cannot be considered as the only determinant of the clinical manifestations of the disease.²¹

(4) Animal experiments indicate that: (a) in the presence of an acute reduction of the lumen of a major coronary branch by 65 per cent, flow across the stenosis can still increase by about five times the resting level²²; (b) only in the presence of a 90 to 95 per cent acute lumen reduction does flow through the stenosed branch decrease below resting level²²; (c) normal myocardial flow distribution was observed in dogs during submaximal treadmill exercise six months after ameroid closure of the left circumflex artery.²³ Thus, functional factors interfering with the relation between myocardial demand and supply, in the presence or absence of coronary atherosclerotic stenosis, must play a role in the genesis of angina pectoris. Similar conclusions were reached by Lewis¹ in relation to attacks of angina at rest. On the basis of careful measurements of heart rate and blood pressure in patients during successive attacks of angina at rest and during physical exertion, Lewis concluded: "It appears almost necessary to assume that a strict relation between pain and pressure is broken by some factors of interference and the factor in mind is an inconstant state of the coronary vessels". However, the hypothesis of coronary vasoconstriction, considered as a cause of angina pectoris long ago by Latham,²⁴ and Osler,²⁵ and other distinguished authors, fell into disrepute when nearly all patients with angina were proved at necropsy to have coronary artery atherosclerotic obstructions of variable severity.²⁶ Because pathologists could document so clearly the atherosclerotic stenosis but were unable to obtain any evidence of vasomotor tone during life in their necropsy specimens, they

felt entitled to deny categorically the existence of other mechanisms that they could not objectively demonstrate.

The hypothesis of coronary vasospasm was proposed by Prinzmetal *et al.* in 1959²⁷ to account for the form of angina that he described as "variant" and which has stimulated more recent research using recent advances in technology.

Studies of angina at rest

Following this line of reasoning, we have concentrated our interest on the study of angina at rest where, according to clinical experience, functional factors might be expected to play a major role.

Typical transient electrocardiographic abnormalities (ST segment depression or elevation greater than 0.2 mV) were documented during at least one spontaneous attack of angina in 193 patients admitted to our institution between 1970 and 1977 with attacks of angina at rest.* In these patients, clinical histories, electrocardiographic changes during angina, and coronary arteriographic findings were extremely variable. The onset of angina ranged from 25 years to a few days before admission to hospital. More than a third had had a previous myocardial infarction and more than two-thirds also gave a history of exertional angina which sometimes preceded, but more often followed, the onset of angina at rest. A minority reported such severe limitation of exercise tolerance that they were consistently prevented from climbing a single flight of stairs or from walking 100 metres at a slow pace.

These patients were the subject of our research, which has developed along five lines.

CONTINUOUS ELECTROCARDIOGRAPHIC MONITORING

With the aim of investigating the pattern of transient electrocardiographic changes and their relation to anginal pain, and to arrhythmias, we recorded over 7000 electrocardiograms during transient ischaemic episodes with or without pain.²⁸

The most striking observations made possible by the large number of episodes of transient myocardial ischaemia recorded were:

- (1) the great variability of the transient electrocardiographic changes in different patients and in the same patient during different episodes and during successive phases of the same episode;

* Patients with typical angina at rest, with or without old myocardial infarction, who did not show typical electrocardiographic changes during their spontaneous attacks of angina, were not included in this group.

- (2) the delayed appearance of pain relative to the onset of electrocardiographic changes;
- (3) the frequency in some patients of typical, transient ST segment and T wave changes, similar to those observed during attacks of angina, which were not accompanied by chest pain, and of T wave changes alone with or without pain.

In those patients in whom unequivocal electrocardiographic changes were documented at least once during angina, elevation of the ST segment (of at least 0.2 mV) in at least one lead, with or without depression in other leads, was more frequent than depression. However, while some patients consistently showed ST segment elevation in the same leads in all episodes, others frequently or occasionally presented with episodes characterised by ST segment depression and/or transitional forms such as peaking of T waves, negative T waves becoming upright, or inversion of positive or flat T waves. Conversely, other patients who usually showed ST segment depression, occasionally showed transient reversible ST segment elevation and/or transitional forms. All these changes were observed with or without anginal pain.

These observations show that (a) elevation of the ST segment, described by Penati,²⁹ Brow and Holman,³⁰ Secondari,³¹ and Wilson and Johnston³² and considered to be the hallmark of the variant form of angina by Prinzmetal,²⁷ appears to be simply the most dramatic aspect of a continuous spectrum of electrocardiographic changes during angina rather than characteristic of a well-defined syndrome²⁸; and (b) anginal pain is not a sensitive index of the presence of acute transient myocardial ischaemia because it occurs late and it may be absent.

STRESS TESTING

Because of the frequent absence of a history of progressive decrease of exercise tolerance to minimal levels, we considered it of great practical relevance to study the coronary flow reserve of these patients. We therefore performed sitting bicycle ergometer exercise stress testing, with continuous supervised monitoring of the electrocardiogram, and of the blood pressure in most patients (initially only in a few and recently in all). More recently, we have studied a group of patients by comparing the values of the heart rate systolic blood pressure product (as an index of myocardial oxygen demand) measured at the onset of the ischaemic episode at rest with that attained at the angina threshold during pacing-induced tachycardia. These studies showed the following:

- (1) The coronary flow reserve of these patients

was usually not reduced to the extremely low levels expected from their history: angina never developed below an exercise level of 50 watts for two minutes and only very few patients developed ST segment depression at 25 watts; most patients could perform up to 75 or 100 watts and several had a negative stress test.²⁸⁻³³

- (2) The heart rate systolic blood pressure product at the onset of the spontaneous attacks of angina was consistently much lower than that attained at the angina threshold during atrial pacing or exercise.³⁴

These observations show that: (a) it is illogical to assume without proof that spontaneous attacks of angina at rest result from an increase in myocardial oxygen demand in excess of that tolerated during the stress test; and (b) two different causes of angina should be postulated to coexist in patients with angina occurring at rest at a much lower level of cardiac work than that causing exertional angina.

CONTINUOUS HAEMODYNAMIC MONITORING

For rational management of these patients we considered it essential to show whether or not the attacks of angina at rest were caused by an increase in the haemodynamic indices which determine myocardial oxygen demand. Thus, in collaboration with Drs Chierchia, Marchesi, Pesola, and Mimmo, we continuously monitored arterial and intracardiac pressures for several hours in patients with frequently recurring attacks of angina. These studies³⁵⁻³⁸ showed the following:

- (1) There was no significant increase in heart rate, systolic blood pressure, or left ventricular contractility (as indicated by left ventricular peak dP/dt) preceding the onset of the ST segment changes, irrespective of their direction (Fig. 1).

(2) An impairment of ventricular function occurred during angina (sometimes with increases in left ventricular end-diastolic pressure up to 50 mmHg); the episodes with a more abrupt onset of ST segment change (usually elevation) were associated with a sequence of haemodynamic changes remarkably similar to those observed in the dog³⁷ after sudden coronary ligation (reduction of peak ventricular relaxation and contraction dP/dt, increase in end-diastolic pressure, drop in systolic pressure, and elevation of the ST segment) (Fig. 1).

- (3) Pain consistently followed (sometimes by several minutes) the onset of the ST segment change; heart rate and blood pressure were sometimes increased at the onset of pain and increased further thereafter.

(4) A large number of transient episodes of typical ST segment elevation or depression, not

accompanied by pain, and of episodes of transient T wave change (peaking, inversion, inverted becoming upright) with and without pain, were recorded, and were associated with impairment of left ventricular function, similar to that occurring during episodes of typical ST segment elevation or depression with pain (Fig. 1).

These observations show that: (a) attacks of angina at rest are not caused by an excessive increase in myocardial demand; this is in contrast to the conclusion reached from studies based on isolated measurements at the onset of the attack of angina.³⁸⁻⁴⁰ This contradiction may be related partly to the erroneous assumption that the onset of pain corresponds to the onset of ischaemia and partly to the assumption that the observation of an increase in heart rate and blood pressure was, by itself, sufficient proof that the coronary flow reserve was indeed exceeded. (b) Asymptomatic ST segment changes and atypical T wave changes may be an expression of acute myocardial ischaemia associated with obvious ventricular functional impairment and sometimes also with dangerous arrhythmia. Thus, pain and ST segment changes

can no longer be considered the only hallmarks of acute myocardial ischaemia.

REGIONAL MYOCARDIAL PERFUSION STUDIES
Following our previous studies we decided to investigate whether these attacks of angina at rest were caused by a sudden transient reduction of regional myocardial perfusion. In collaboration with Drs Padodi, Severi, and Uthurralt, we performed thallium-201 scintigraphic studies during attacks of angina at rest in a large number of patients with a variety of transient electrocardiographic changes, with or without pain.

A regional reduction of myocardial perfusion was consistently documented regardless of the direction of the ST segment or T wave change and of the presence or absence of pain. Regional reduction of myocardial perfusion was massive and transmural during episodes characterised by elevation of the ST segment, and corresponded well with the leads involved by ST segment elevation,⁴¹ but similar massive deficits of tracer uptake were also seen in patients with only transient ST segment shifts towards normal or peaking of T waves, with or

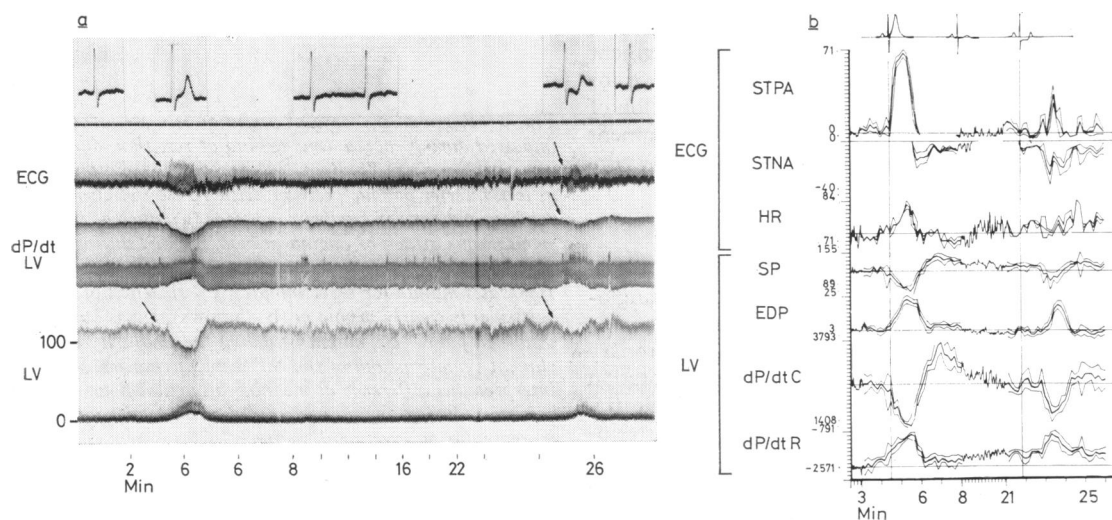


Fig. 1 Transient episodes of acute myocardial ischaemia with ST segment elevation and depression may occur in the same leads within a few minutes, without symptoms. Continuous haemodynamic recording (in a patient who had episodes of angina with ST segment elevation and episodes with ST depression) (a) and computer analysis (b). During the recording, the patient had several episodes of angina with variable electrocardiographic changes; some electrocardiographic changes were asymptomatic. This recording shows two successive asymptomatic episodes characterised by haemodynamic changes similar to those observed during symptomatic episodes. In (a), the onset of the changes is indicated by arrows. In (b), the onset of the episodes of ST segment elevation and depression (vertical lines) is not preceded by any increase in heart rate, systolic blood pressure, or contractility. The presence of these electrocardiographic abnormalities is associated with impairment of dP/dt, and with increase in diastolic and reduction in systolic pressure of the left ventricle. STPA and STNA, positive and negative area of the ST segment of the electrocardiogram; HR, heart rate; dP/dt C and R, peak contraction and relaxation dP/dt.

without angina. Less massive, more diffuse deficits of thallium-201 uptake were observed during episodes characterised by ST segment depression, a pattern compatible with diffuse subendocardial ischaemia.⁴²⁻⁴³ Patients with attacks of angina with ST segment depression, occurring either spontaneously at rest or during an effort test, showed much more obvious deficits of thallium uptake during spontaneous than during exercise-induced attacks (Fig. 2), indicating a reduction of regional myocardial perfusion during spontaneous angina and an inadequate increase during exertional angina.⁴⁴

More recently, Chierchia *et al.*,⁴⁵ in a study based on continuous monitoring of coronary sinus oxygen saturation, showed that transient ST segment changes and transient T wave changes, with or without pain, were not only accompanied by a reduction in regional myocardial perfusion, as shown by thallium-201 studies, but were also preceded by a sudden regional reduction of coronary blood flow.

From these observations it follows that: (a) the acute imbalance responsible for the attacks of angina at rest is caused by a sudden transient reduction of regional coronary blood supply rather than by an excessive increase in myocardial metabolic demand; and (b) a massive, transmural reduction of flow seems to result in ST segment elevation, inverted T waves becoming positive, or peaking of T waves; a non-transmural reduction of flow seems to result in depression of the ST segment or in T wave inversion, irrespective of the occurrence of pain.

CORONARY ARTERIOGRAPHY

Stimulated by the hypothesis of Latham,²⁴ Osler,²⁵ and Prinzmetal *et al.*²⁷ and isolated fortuitous angiographic observations,⁴⁶⁻⁴⁹ we began a systematic investigation of the possible role of coronary vasospasm in angina at rest. Thus, in collaboration with Drs L'Abbate, Pesola, Marzilli, and Ballestra, we obtained repeated selective coronary arteriograms during attacks of angina either spontaneous or induced by the intravenous injection of ergometrine, with the aim of demonstrating the occurrence of coronary vasospasm and of determining its site and its relation to coronary atherosclerotic stenosis and to transient electrocardiographic changes.

In the absence of symptoms or electrocardiographic signs of acute myocardial ischaemia, coronary arteriograms (obtained in about 80% of these patients) showed normal vessels or no critical stenoses in about 10 per cent, triple vessel disease in about 30 per cent, and one or two vessel disease

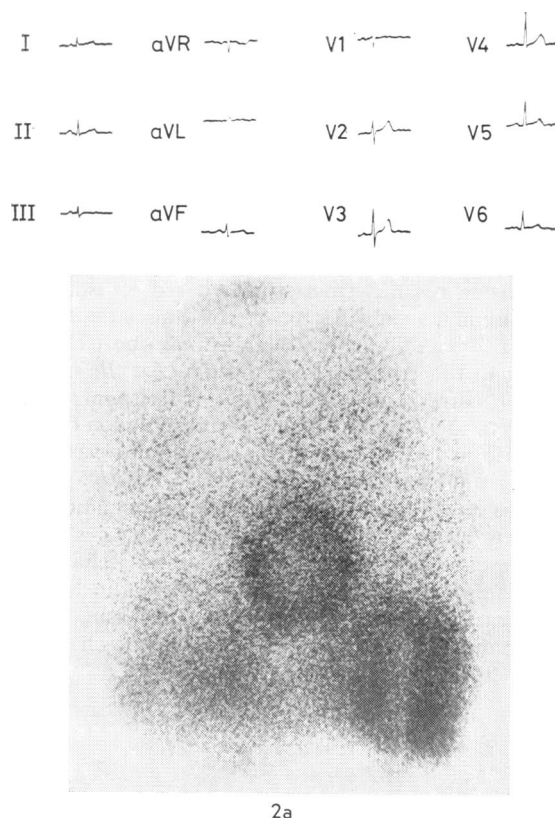
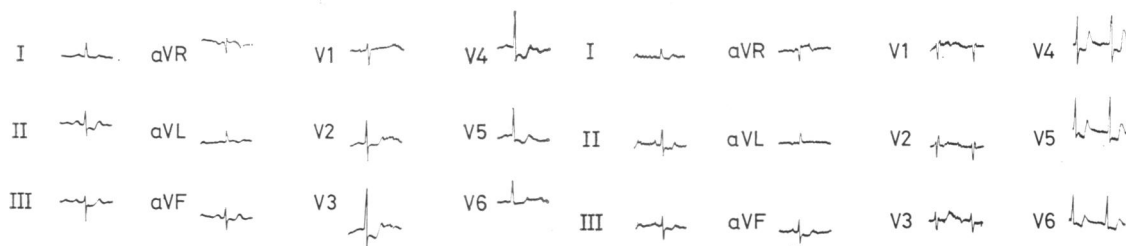


Fig. 2 Regional myocardial perfusion is more severely impaired during spontaneous angina at rest than during exertional angina. Thallium-201 myocardial scintigraphy in left anterior oblique position, with 12 lead electrocardiogram (top) in control conditions (a), during spontaneous attack of angina at rest (b), and during angina occurring during exercise stress test at 100 watts/minute for three minutes (c). A deficit of perfusion is clearly visible in (b) (arrows), but is barely visible in panel (c), notwithstanding the similarity of the clinical symptoms and of the ST segment changes. We interpret this difference as meaning an actual flow reduction during angina at rest and to an inadequate increase during exertional angina.

in the remainder.²⁸ Severe coronary stenoses were found more often in those patients who also gave a history of exertional angina.

When contrast injections were made during an episode of transient ST segment change, with or without pain, transient vasospasm was observed in each case.^{28 50-53} The severity and extent of spasm, the electrocardiographic abnormalities, and the degree of atherosclerosis in the vessel showing spasm were variable. Variable severity and extent



2b

2c

of spasm was seen not only in different phases of the ischaemic episode, but also in successive episodes. Giant ST segment elevation was always associated with occlusive spasm of a main branch (main right, left anterior descending, circumflex) without distal filling, but similar angiographic appearances were associated also with lesser degrees of ST segment elevation, with peaking of T waves, and with negative T waves becoming upright (Fig. 3). In other instances these less-dramatic electrocardiographic abnormalities were associated with subocclusive spasm, with poor distal filling, sometimes retrograde via collaterals, and slow run-off. Often diffuse constriction of a branch coronary artery, noticed at the very beginning of an episode when there was only peaking of T waves, was followed by complete occlusion during obvious elevation of the ST segment.^{28 51}

Typical widespread ST segment depression was associated with diffuse but less severe spasm of many branches, or with occlusive or subocclusive spasm of a large branch with severe atherosclerotic stenosis and some distal filling via collaterals. Conversely, isolated spasm of a diagonal or of a

septal branch was observed in patients with isolated ST segment depression in the anteroseptal or anterior leads.^{28 51 52}

Vasospasm was observed in vessels which were normal on angiograms, or which had wall irregularities only, or stenosis varying from 50 per cent to subocclusive.

Usually the vasospasm appeared to extend proximally and, when visible, also distally from the stenosis. Retrograde filling via collaterals of the vessel occluded by spasm was observed during some ischaemic episodes. Recently we failed to detect obvious spasm during spontaneous anginal attacks in one patient with severe coronary atherosclerosis; it is possible that a minor reduction in calibre, not easily detectable, may be sufficient to reduce the flow in these cases or that other mechanisms are responsible for the attack.

These observations indicate that:

- (a) coronary vasospasm is responsible in the great majority of cases for the sudden reduction of myocardial blood supply documented by the flow studies;

- (b) the vasospasm may involve vessels with any degree of coronary atherosclerosis. While patients with insignificant organic coronary artery stenosis have an unimpaired exercise tolerance, those with severe stenoses may also develop acute myocardial ischaemia when myocardial demand is increased beyond the coronary flow reserve. Thus, in some patients vasospastic angina may coexist with classical exertional angina; and
- (c) the more frequent documentation of spasm during episodes of ST segment elevation can be attributed to the more dramatic changes in calibre of the main branches associated with this electrocardiographic pattern. In vessels with critically narrowed lumen, a small increase in vasomotor tone, not easily detectable angiographically, may be sufficient to reduce flow. In other cases constriction of resistance vessels may be responsible for the reduction in flow.

A distinction between spasm of large branches, increase in normal vasomotor tone, and constriction of resistance vessels may be relevant, because if different mechanisms are responsible, different specific treatments may be required. Platelet aggregation or other mechanisms cannot be assessed angiographically.

Perspective

Each of our five lines of research has yielded results which are in agreement with those of other similar studies.⁵⁴ These confirm the variability of the electrocardiographic changes,⁵⁵ the reasonably good coronary flow reserve,⁵⁶ the absence of increased myocardial demand,⁵⁷⁻⁵⁹ the reduction in regional myocardial perfusion,⁶⁰⁻⁶² and the presence of coronary vasospasm during ST segment elevation⁶³ and depression.⁵⁹⁻⁶⁴ The greater number of reports of angiographic demonstration of spasm during

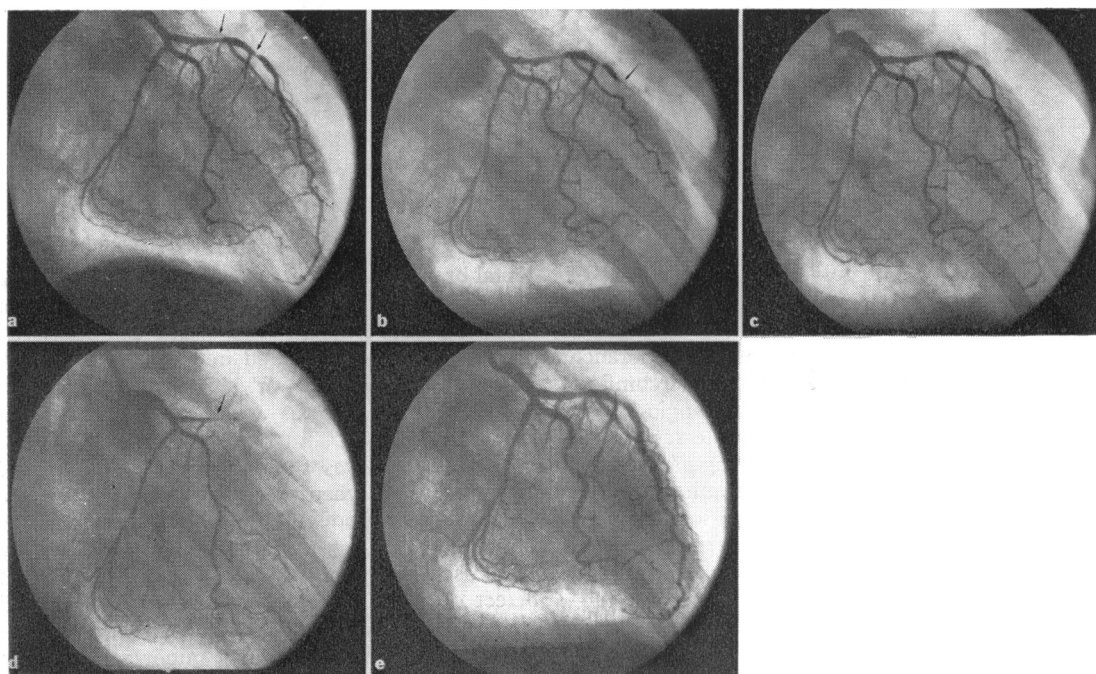


Fig. 3 Coronary spasm may involve different parts of an artery and result in different electrocardiographic changes. The left coronary angiogram in the absence of symptoms shows two stenoses (arrows) in the left anterior descending (LAD) (a). The patient also had angina during severe exertion; the triangular electrocardiographic stress test became positive only at 150 watts every two minutes (workload increased every two minutes during continuous exercise without intermission), but he also had recurrent attacks of angina at rest with variable ST segment changes. Angiography during asymptomatic T wave elevation in V4 (b) showed occlusive spasm in the middle third of the LAD (arrow) which disappeared spontaneously within a few minutes (c); about five minutes later he had spontaneous ST segment elevation with pain and showed occlusive spasm of the proximal LAD (d, arrow) which disappeared after intracoronary isosorbide dinitrate (0.2 mg) which caused evident coronary dilatation (e).

episodes of ST segment elevation is probably attributable to the particular interest in this electrocardiographic pattern stimulated by the hypothesis of Prinzmetal *et al.*,²⁷ and to the more dramatic changes in calibre of the main coronary branches usually associated with this electrocardiographic pattern.

The results of these five lines of research fit together, like tesserae of a mosaic, to provide a clearer picture of angina pectoris. Therefore, I believe that the time has come to attempt a re-definition and a pathogenetic classification of angina pectoris which is both clinically useful and a stimulus to research.

REDEFINITION OF ANGINA PECTORIS

In the context of ischaemic heart disease angina pectoris appears to represent only a clinical syndrome, one of the possible manifestations of acute transient myocardial ischaemia, which may be completely asymptomatic, or may be accompanied by dyspnoea only or by rhythm disturbances only: it can result from various pathogenetic mechanisms and can be associated with various electrocardiographic changes. Anginal pain does not even seem necessarily to indicate a greater severity of ischaemia or risk of dangerous arrhythmias. Therefore, since management of angina has hitherto been inspired by the traditional concept of excessive increase of metabolic demand and since our studies have shown that this is not the only cause, a provisional updating of the classification of angina should help in the practical management of the patient.

CLASSIFICATION OF ANGINA PECTORIS

The clinical classification into "stable" and "unstable" angina has a prognostic significance only and serves as a guide to how carefully and intensively the patient should be managed rather than what type of management he should receive. I would like to propose the following provisional pathogenetic classification: angina "secondary" to increased myocardial demands beyond the fixed possibility of supply limited by coronary atherosclerotic stenosis (according to the now prevailing theory) and "primary" angina,* caused by other mechanisms.⁶⁵ This distinction should simply serve the purpose of an immediate clear-cut separation of the traditionally accepted mechanism of "secondary" angina, for which the diagnostic and thera-

peutic approaches are already reasonably well defined, from all other causes which require appropriate and specific management. As in the case of systemic hypertension, the pathogenetic classification will become more precise as the causes of "primary" angina become identified.

For practical management, patients should be classified as having (1) only "primary" angina; (2) only "secondary" angina; (3) predominantly "primary" or predominantly "secondary" angina (with or without transient electrocardiographic changes and with or without associated episodes of asymptomatic transient myocardial ischaemia). The mechanisms of "primary" angina and the degree of limitation of exercise tolerance in "secondary" angina (as a measure of the degree of limitation of the coronary flow reserve) should also be specified (Table).

For "primary" angina the only reasonably well-documented cause so far is coronary vasospasm, possibly because it has been more carefully sought than other postulated causes such as platelet aggregation,⁶⁶ small vessel disease,⁶⁷ transient myocardial metabolic abnormalities,⁶⁸ and inadequate vasodilatation.⁶⁹

Table Classification of angina pectoris*

Pathogenetic mechanisms	Severity
1) "Primary" angina	Depends on: number and duration of the attacks, incidence of severe arrhythmias
— Vasospastic	
— ?	
— ?	
(2) "Secondary" angina	<p>Grade 1: angina occurs consistently and only during severe exertion</p> <p>Grade 2: angina occurs consistently during moderate exertion (fast walk for half a mile, climbing rapidly several flights of stairs); higher levels of work are never tolerated; lesser exertion never causes angina under ordinary conditions</p> <p>Grade 3: angina occurs consistently during lesser exertion (walking 100 yards, climbing one or two flights of stairs); higher levels of work are never tolerated; lower levels of exertion never cause angina under ordinary conditions</p> <p>Grade 4: angina occurs consistently with the slightest physical exertion (walking a corridor); higher levels of activity are never tolerated; angina may also be caused by increased heart activity at rest</p>
(3) Mixed forms	Combined criteria of "primary" and of "secondary" angina; patients who have a widely variable threshold of exertional angina or have also spontaneous attacks (not provoked by obvious haemodynamic changes) should be suspected of having mixed forms
— predominantly "primary"	
— balanced	
— predominantly "secondary"	

* "Primary" is a term borrowed from other fields of medicine meant only to indicate our present ignorance about pathogenesis. It is expressly used to emphasise that this differentiation, rather than the proof of the existence of spasm, is the most important message of our expanding views on the mechanisms of angina pectoris. It is meant to stimulate an open-minded approach to any possible cause of angina.

* Patients may have variable electrocardiographic changes during angina and may also have asymptomatic episodes of transient acute myocardial ischaemia.

In "secondary" angina, the severity of impairment of coronary flow reserve should be evaluated from a careful history and from the level of cardiac work at which the electrocardiographic stress test is consistently positive; the level of exertion that the patient can never exceed without the occurrence of symptoms or signs of acute myocardial ischaemia should be used to classify patients. The diagnosis of "secondary" angina should be confirmed by the demonstration of the presence of critical coronary stenoses.

With careful evaluation, the vast majority of patients we see fall into the third category and the minority into the second category listed in the Table.

RESEARCH APPROACH

New practical objective criteria for the diagnosis of transient acute myocardial ischaemia are needed. In fact, the low sensitivity of the traditional hallmarks of acute transient myocardial ischaemia, namely pain and ST segment changes, suggests a reconsideration of our set of equations: pain + ST segment changes = ischaemia; pain + atypical electrocardiographic changes, or ST segment changes - angina = uncertain; atypical ST segment changes - pain = no ischaemia.

It is inappropriate to discuss the "sensitivity" and "specificity" of electrocardiographic stress testing or of myocardial perfusion studies in predicting the presence or absence of coronary atherosclerotic lesions, because these tests are sensitive to ischaemia, which is not necessarily related to the presence of significant organic coronary lesions. In particular, these tests will not detect severe organic lesions if the latter are unaccompanied by ischaemia and, conversely, they will be positive in the presence of ischaemia even in the absence of significant organic coronary lesions.

The objective demonstration of the existence of vasospastic ischaemia should stimulate similar extensive studies for other possible pathogenetic mechanisms.

The prevalence of symptomatic and asymptomatic vasospastic acute myocardial ischaemia in ischaemic heart disease, its natural history,^{28 70-72} and its role in the genesis of acute myocardial infarction and sudden coronary death,^{28 72} should be investigated.

The identification of the causes of vasospasm, still largely controversial,^{41 73-76} and of the factors that control the reversibility or irreversibility of vasospasm, is required for rational treatment and prevention. Meanwhile, the efficacy of symptomatic treatment in reducing or preventing angina attacks in patients with "primary" angina should be evaluated by means of repeated cross-over trials in

individual patients,^{77 78} rather than the usual double-blind studies in groups of patients, because of the possible individual differences in the aetiology of the disease and because spontaneous waxing and waning of symptoms often occur in these patients.

CLINICAL APPROACH

A careful history, continuous electrocardiographic monitoring, and electrocardiographic stress testing are at present the most valuable practical methods for the diagnosis of acute transient myocardial ischaemia. In those patients in whom a positive diagnosis can be made, the observation of whether angina occurs at a fixed or a variable threshold of cardiac work, is the first clue to a diagnosis of "primary" or "secondary" angina.

In secondary angina the assessment of the degree of impairment of coronary flow reserve, from carefully recorded history and by repeated electrocardiographic stress tests, provides the indication for coronary arteriography, performed with a view to coronary surgery. Only patients with severe secondary angina are potential candidates for coronary surgery for the treatment of their symptoms. Whether or not other patients are candidates for coronary surgery for improvement of prognosis is not one I can deal with now.

In primary angina, according to our experience, a vasospastic origin should be suspected in those patients with unstable angina at rest. However, patients with stable angina were also shown to have attacks of primary angina during ordinary daily activity,⁷⁹ and vasospasm has recently been demonstrated during stress testing^{80 81} and cold exposure.⁸² In fact, elevation of the ST segment, a reasonably reliable hallmark of acute vasospastic ischaemia, is sometimes observed during exertion.^{28 83-86} Vasospasm can be demonstrated angiographically, by myocardial perfusion studies, and by reproducing electrocardiographic changes by provocative tests, which seem to have high specificity, but unknown sensitivity.⁸⁷⁻⁸⁹ As a treatment of primary vasospastic angina, beta-blockers, the most widely used antianginal drugs, do not have the same rational indications as they do in secondary angina; they were found to be effective in some patients, but only at doses much higher than those sufficient to produce complete beta-blockade.⁹⁰ Nitrates and calcium antagonists^{40 91} appear at present to be the most effective drugs in the treatment of vasospastic primary angina. Coronary bypass surgery does not appear to be a reasonable approach for relieving symptoms for patients with primary angina "unresponsive" to medical treatment, though in some patients operation might result in symptomatic relief as has been observed in the case of other now

obsolete surgical procedures. Patients with mixed forms of angina may be candidates for bypass surgery, after medical control of their spontaneous attacks, if their exercise tolerance is much impaired. In a recent study,⁹² coronary vasospasm has been shown to occur after bypass surgery, cardiac denervation, and autotransplantation. Prognosis depends on the one hand on the intensity and frequency of occurrence of vasoconstriction, and on the other hand on the underlying severity of coronary atherosclerosis, because any functional mechanism capable of reducing myocardial perfusion may be expected to have a more devastating effect in the presence of organic lesions.

References

- ¹Lewis T. Angina pectoris associated with high blood pressure and its relief by amyl nitrite: with a note on Nothanagel's syndrome. *Heart* 1931; **15**: 305-27.
- ²Friedberg CK. *Diseases of the heart*. 3rd ed. New York: Saunders, 1966.
- ³James TN. Angina without coronary disease (sic). *Circulation* 1970; **42**: 189-91.
- ⁴Maseri A. Expanding views on coronary artery disease: the role of vasospasm and other modulatory factors. In: Hegyely R, ed. *Atherosclerosis reviews*. New York: Raven Press, 1980: 271-9.
- ⁵Gorlin R. Angiographic coronary artery findings in patients with typical angina relative to those with myocardial infarction and those with suspect disease only. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 71-4.
- ⁶Bertolasi CA, Tronze JE, Carreno CA, Jalon J, Ruda Vega M. Unstable angina. Prospective and randomised study of its evolution, with and without surgery. *Am J Cardiol* 1974; **33**: 201-8.
- ⁷National cooperative study group to compare medical and surgical therapy in unstable angina pectoris. I. Report of protocol and patient population. *Am J Cardiol* 1976; **37**: 896-902.
- ⁸Likoff W, Kasparan H, Segal BL, Worack P, Lehman JS. Clinical correlation of coronary arteriography. *Am J Cardiol* 1965; **15**: 159-64.
- ⁹Paulin S. Coronary angiography: a technical, anatomic and clinical study. *Acta Radiol* 1964; suppl 233.
- ¹⁰Campeau L, Bourassa MG, Bois MA, et al. Clinical significance of selective coronary cineangiography. *Can Med Assoc J* 1968; **99**: 1063-8.
- ¹¹Proudfit WL, Shirey EK, Sones FM Jr. Distribution of arterial lesions demonstrable by selective cine-coronary arteriography. *Circulation* 1967; **36**: 54-62.
- ¹²Hultgren H, Calciano A, Platt R, Abrams H. A clinical evaluation of coronary arteriography. *Am J Med* 1967; **42**: 228-47.
- ¹³Proudfit WL, Shirey EK, Sheldon WC, Sones FM Jr. Certain clinical characteristics correlated with extent of obstructive lesions demonstrated by cinecoronary arteriography. *Circulation* 1968; **38**: 947-54.
- ¹⁴Friesinger DC, Smith RF. Correlation of electrocardiographic studies and arteriographic findings with angina pectoris. *Circulation* 1972; **46**: 1173-84.
- ¹⁵Fuster V, Frye RL, Connolly DC, Danielson MA, Elvessack LR, Kurland LT. Arteriographic patterns early in the onset of the coronary syndromes. *Br Heart J* 1975; **37**: 1250-5.
- ¹⁶Neill WA, Ritzmann LW, Selden R. The pathophysiologic basis of acute coronary insufficiency. Observations favouring the hypothesis of intermittent reversible coronary obstruction. *Am Heart J* 1977; **94**: 439-44.
- ¹⁷Redwood DR, Epstein SE. Uses and limitations of stress testing in the evaluation of ischaemic heart disease. *Circulation* 1972; **46**: 1115-31.
- ¹⁸Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea: preliminary report. *JAMA* 1953; **152**: 1090-3.
- ¹⁹Allison RB, Rodriguez FL, Higgins EA Jr, et al. Clinicopathologic correlations in coronary atherosclerosis. *Circulation* 1963; **27**: 170-84.
- ²⁰Baroldi G, Scmazzone G. *Coronary circulation in the normal and pathologic heart*. Washington, DC: American Registry of Pathology, Armed Forces Institute of Pathology, Government Printing Office, 1967.
- ²¹Maseri A. Myocardial blood flow in acute ischaemia and its measurement. In: Oliver MF, ed. *Modern trends in cardiology*. London: Butterworths, 1974: 115-53.
- ²²Gregg DE, Bedynek JL Jr. Compensatory changes in the heart during progressive coronary artery stenosis. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 3-11.
- ²³Lambert PR, Hess DS, Bache RJ. Effect of exercise on perfusion of collateral-dependent myocardium in dogs with chronic coronary artery occlusion. *J Clin Invest* 1977; **59**: 1-7.
- ²⁴Latham PM. *Collected works*, vol I. London: New Sydenham Society, 1876: 445-80.
- ²⁵Osler W. Lumleian lectures on angina pectoris, Lecture I. *Lancet* 1910; **i**: 697-702.
- ²⁶Blumgart HL, Schlesinger MJ, Davis D. Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis and myocardial infarction to the pathological findings. With particular reference to the significance of the collateral circulation. *Am Heart J* 1940; **19**: 1-91.
- ²⁷Prinzmetal M, Kennamer R, Merliss R, Wada T, Bor N. Angina pectoris. 1. A variant form of angina pectoris. *Am J Med* 1959; **27**: 375-88.
- ²⁸Maseri A, Severi S, De Nes M, et al. "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischaemia. Pathogenetic mechanisms, estimated incidence, clinical and coronarographic findings in 138 patients. *Am J Cardiol* 1978; **42**: 1019-35.
- ²⁹Penati F. Le modificazioni dell'elettrocardiogramma nelle crisi di angina di petto ed il loro significato nella patogenesi delle crisi stesse. *Minerva Med* 1934; **2**: 289-98.

- ³⁰Brow GR, Holman DV. Electrocardiographic study during a paroxysm of angina pectoris. *Am Heart J* 1933; **9**: 259-64.
- ³¹Secondari E. Studio elettrocardiografico dell'attacco anginoso. *Cuore Circol* 1938; **22**: 341-54.
- ³²Wilson EN, Johnston FD. The occurrence in angina pectoris of electrocardiographic changes similar in magnitude and in kind to those produced by myocardial infarction. *Am Heart J* 1941; **22**: 375-88.
- ³³Severi S, Davies G, L'Abbate A, Maseri A. Long-term prognosis of variant angina with medical management. *Circulation* 1979; **II**: 250.
- ³⁴Biagini A, Rovai D, Maseri A, *et al.* Comparison of the double product determined during angina at rest and during atrial pacing. Diagnostic significance. First Joint Meeting of the Working Groups of the European Society of Cardiology, Brighton (abstract). *Trans Eur Soc Cardiol* 1978; **1**: 194.
- ³⁵Maseri A, Pesola A, Mimmo R, Chierchia S, L'Abbate A. Pathogenetic mechanisms of angina at rest (abstract). *Circulation* 1975; **51** & **52**, suppl 2: 89.
- ³⁶Chierchia S, Marchesi C, Maseri A. Evidence of angina not caused by increased myocardial metabolic demand and patterns of electrocardiographic and haemodynamic alterations during "primary" angina. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 145-55.
- ³⁷Vatner SF, Millard RW, Patrick TA, Heyndrickx GR. Effects of isoproterenol on regional myocardial function, electrogram and blood flow in conscious dogs with myocardial ischaemia. *J Clin Invest* 1976; **57**: 1261-71.
- ³⁸Roughgarden JW, Newman EV. Circulatory changes during the pain of angina pectoris. 1772-1965. A critical review. *Am J Med* 1966; **41**: 935-46.
- ³⁹Robinson BF. Relation of heart rate and systolic pressure to the onset of pain and angina pectoris. *Circulation* 1967; **35**: 1073-83.
- ⁴⁰Littler WA, Honour AJ, Sleight P, Stott FD. Continuous recording of direct arterial pressure and electrocardiogram in unrestricted man. *Br Med J* 1972; **iii**: 76-8.
- ⁴¹Maseri A, Parodi O, Severi S, Pesola A. Transient transmural reduction of myocardial blood flow, demonstrated by thallium-201 scintigraphy, a cause of variant angina. *Circulation* 1976; **54**: 280-8.
- ⁴²Parodi O, Severi S, Uthurralt N, Solfanelli S, Maseri A. Angina pectoris at rest: regional myocardial perfusion during ST segment elevation or depression (abstract). *Circulation* 1977; **55** & **56**: 229.
- ⁴³Parodi O, Severi S, Maseri A, Biagini A. Reversible reduction of regional myocardial blood flow as cause of "primary" angina at rest, relation with electrocardiographic S-T changes. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 227-37.
- ⁴⁴Uthurralt N, Parodi O, Maseri A, Severi S, Michelassi C, Bencivelli V. Myocardial scintigraphy in patients with angina at rest. Studies during spontaneous and exercise induced attacks. First Joint Meeting of the Working Groups of the European Society of Cardiology, Brighton, UK (abstract). *Trans Eur Soc Cardiol* 1978; **1**: 137.
- ⁴⁵Chierchia S, Maseri A, Simonetti I, Brunelli C. O₂ myocardial extraction in angina at rest. Evidence of a primary reduction of blood supply (abstract). *Circulation* 1977; **55** & **56**, suppl III: 37.
- ⁴⁶Gensini GC, Di Giorgio S, Murad-Netto S, Black A. Arteriographic demonstration of coronary artery spasm and its release after the use of a vasodilator in a case of angina pectoris and in the experimental animal. *Angiology* 1962; **13**: 550-3.
- ⁴⁷Dhurander RW, Watt DL, Silver MD, Trimble AS, Adelman AG. Prinzmetal's variant form of angina with arteriographic evidence of coronary arterial spasm. *Am J Cardiol* 1972; **30**: 902-5.
- ⁴⁸MacAlpin RN, Kattus AA, Alvaro AB. Angina pectoris at rest with preservation of exercise capacity: Prinzmetal's variant angina. *Circulation* 1973; **47**: 946-58.
- ⁴⁹Oliva RB, Potts DE, Pluss RG. Coronary arterial spasm in Prinzmetal angina: documentation by coronary arteriography. *N Engl J Med* 1973; **288**: 745-51.
- ⁵⁰Maseri A, Mimmo R, Chierchia S, Marche C, Pesola A, L'Abbate A. Coronary spasm as a cause of acute myocardial ischaemia in man. *Chest* 1975; **68**: 625-33.
- ⁵¹Maseri A, L'Abbate A, Ballestra AM, *et al.* Coronary vasospasm in angina pectoris. *Lancet* 1977; **i**: 713-7.
- ⁵²Marzilli M, L'Abbate A, Ballestra M, Maseri A. Coronary angiography findings during angina at rest with ST depression (abstract). *Circulation* 1977; **55** & **56**, suppl III: 83.
- ⁵³Pesola A, Ballestra AM, De Nes M. Evidence of coronary spasm in man during "primary" angina at rest. Relation to the site of atherosclerotic stenosis. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 239-46.
- ⁵⁴Hillis LD, Braunwald E. Coronary-artery spasm. *N Engl J Med* 1978; **299**: 695-702.
- ⁵⁵Jouve A, Quiran JB, Viallet H, *et al.* Les modifications électrocardiographiques au cours des crises d'angor spontané. *Arch Mal Coeur* 1969; **62**: 331-51.
- ⁵⁶Berndt TB, Fitzgerald J, Harrison DC, Schroeder JS. Haemodynamic changes at the onset of spontaneous versus pacing-induced angina. *Am J Cardiol* 1977; **39**: 784-8.
- ⁵⁷Guazzi M, Polese A, Fiorentini C, Magrini F, Bartorelli C. Left ventricular performance and related haemodynamic changes in Prinzmetal's variant angina pectoris. *Br Heart J* 1971; **33**: 84-94.
- ⁵⁸Guazzi M, Polese A, Fiorentini C, Magrini F, Olivari MT, Bartorelli C. Left and right heart haemodynamics during spontaneous angina pectoris. Comparison between angina with ST segment depression and angina with ST segment elevation. *Br Heart J* 1975; **37**: 401-13.
- ⁵⁹Tavazzi L, Salerno JA, Ray M, *et al.* Acute myocardial ischaemia induced by ergonovine maleate in patients with "primary" angina. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 247-63.
- ⁶⁰Berman ND, McLaughlin PR, Huckell VF, Mahon

- WH, Morch JE, Adelman AG. Prinzmetal's angina with coronary artery spasm. Angiographic, pharmacologic, metabolic and radionuclide perfusion studies. *Am J Med* 1976; **60**: 727-32.
- ⁶¹McLaughlin PR, Doherty PW, Martin RP, Goris ML, Harrison DC. Myocardial imaging in a patient with reproducible variant angina. *Am J Cardiol* 1977; **39**: 126-9.
- ⁶²Ricci DR, Orlick AE, Doherty PW, Cipriano PR, Harrison DC. Reduction of coronary blood flow during coronary artery spasm occurring spontaneously and after provocation by ergonovine maleate. *Circulation* 1978; **57**: 392-5.
- ⁶³Meller H, Pickard A, Dack S. Coronary arterial spasm in Prinzmetal's angina: a proved hypothesis. *Am J Cardiol* 1976; **37**: 938-40.
- ⁶⁴Wiener L, Kasprian H, Duca PR, et al. Spectrum of coronary arterial spasm. Clinical, angiographic and myocardial metabolic experience in 29 cases. *Am J Cardiol* 1976; **38**: 945-55.
- ⁶⁵Maseri A. Preface. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: XIII-XIV.
- ⁶⁶Mustard JF, Rowell WC, Murphy EM. Reversible platelet aggregation and myocardial ischaemia (abstract). *Circulation* 1964; **29** & **30**, suppl III: 23.
- ⁶⁷James TN. Pathology of small coronary arteries. *Am J Cardiol* 1967; **20**: 679-91.
- ⁶⁸Richardson PJ, Jackson G, Olsen EGJ, Oram S. Angina pectoris with normal coronary arteriograms: a metabolic problem? In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina pectoris*. New York: Grune & Stratton, 1978: 297-301.
- ⁶⁹Kubler W, Opherk D, Mehmehl H, Zebe D, Maures W. Significance of coronary reserve in patients with different forms of "ischaemic heart disease". In: *VIII World Congress of Cardiology, Tokyo*, Abstract Book I, 1978: 124: 0155.
- ⁷⁰Ballestra AM, L'Abbate A, Marzilli M, Pesola A, Maseri A. Clinical and arteriographic characteristics and follow-up of 44 patients with documented coronary artery spasm. In: *VIII Congress of Cardiology, Tokyo*, Abstract Book I, 1978: 0448.
- ⁷¹Severi S, Davies G, Maseri A, Marzullo P, L'Abbate A. Long term prognosis of "variant" angina on medical treatment. *Am J Cardiol* 1979. In the press.
- ⁷²Maseri A, L'Abbate A, Baroldi G. Coronary vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study of "preinfarction" angina. *N Engl J Med* 1978; **299**: 1271-8.
- ⁷³Yasue H, Touyama M, Simamoto M, Kato H, Tanaka S, Akiyama F. Role of autonomic nervous system in the pathogenesis of Prinzmetal's variant form of angina. *Circulation* 1974; **50**: 534-9.
- ⁷⁴Endo M, Kanda I, Hosoda S, Hayashi H, Hirose K, Konno S. Prinzmetal's variant form of angina pectoris: re-evaluation of mechanisms. *Circulation* 1975; **52**: 33-37.
- ⁷⁵Maseri A, Severi S, Chierchia S, Parodi O, Biagini A. Characteristics and pathogenetic mechanism of "primary" angina at rest. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina*. New York: Grune & Stratton, 1978: 265-73.
- ⁷⁶Maggini C, Guazzelli M, Mauri M, Chierchia S, Cassano GB, Maseri A. Relation of transient myocardial ischaemia to the sleep pattern in patients with "primary" angina. In: Maseri A, Klassen GA, Lesch M, eds. *Primary and secondary angina*. New York: Grune & Stratton, 1978: 157-67.
- ⁷⁷Parodi O, Maseri A, Simonetti I. Management of unstable angina by verapamil. A double-blind crossover study in CCU. *Br Heart J* 1978; **41**: 167-74.
- ⁷⁸Distante A, Maseri A, Severi S, Biagini A. Management of vasospastic "crescendo" angina by continuous infusion of isosorbide dinitrate. *Am J Cardiol* 1979; **44**: 533-9.
- ⁷⁹Schang SJ Jr, Pepine CJ. Transient asymptomatic S-T segment depression during daily activity. *Am J Cardiol* 1977; **39**: 396-402.
- ⁸⁰Montemartini C, Specchia G, De Servi S, et al. Coronary arterial spasm as a cause of exercise-induced S-T segment elevation in patients with variant angina. *Circulation* 1979; **59**: 948-54.
- ⁸¹Yasue H, Omote S, Takizawa A, Nagao M, Miwa K, Tanaka S. Circadian variation of exercise capacity in patients with Prinzmetal's variant angina: role of exercise-induced coronary arterial spasm. *Circulation* 1979; **59**: 938-48.
- ⁸²Mudge GM Jr, Grossman W, Millis R, Lesch M, Braunwald E. Reflex increase in coronary vascular resistance in patients with ischaemic heart disease. *N Engl J Med* 1977; **295**: 1333-7.
- ⁸³Fortuin NJ, Friesinger GC. Exercise-induced S-T segment elevation. *Am J Cardiol* 1970; **49**: 459-64.
- ⁸⁴Bobba P, Vecchio C, Di Guglielmo L, Salerno J, Caseri A, Montemartini C. Exercise-induced S-T elevation. Electrocardiographic and angiographic observations. *Cardiology* 1972; **57**: 162-71.
- ⁸⁵Detry JMR, Menges P, Rousseau MF, Cosyns J, Ponlot R, Brasseur LA. Maximal exercise testing in patients with spontaneous angina pectoris associated with transient S-T segment elevation. Risk and electrocardiographic findings. *Br Heart J* 1975; **37**: 897-903.
- ⁸⁶Chahine RA, Raizner AE, Ishimori T. The clinical significance of exercise induced S-T segment elevation. *Circulation* 1976; **54**: 209-13.
- ⁸⁷Endo M, Hirose K, Keneko N, Hase K, Inoue Y, Konno S. Prinzmetal's variant angina: coronary arteriogram and left ventricular during angina attack induced by methacholine. *N Engl J Med* 1976; **294**: 252-5.
- ⁸⁸Curry RC Jr, Pepine CJ, Sabom MB, Feldman RL, Christie LG, Conti CR. Effects of ergonovine in patients with or without coronary artery disease. *Circulation* 1977; **56**: 803-9.
- ⁸⁹Helfant R. Coronary arterial spasm and provocative testing in ischaemic heart disease. *Am J Cardiol* 1978; **41**: 787-9.
- ⁹⁰Guazzi M, Fiorentini C, Polese A, Magrini F, Olivari MT. Use of beta-receptor antagonists in spontaneous angina pectoris. In: Maseri A, Klassen GA, Lesch M, eds. *Pathogenetic mechanisms of angina pectoris*. New York: Grune & Stratton, 1978: 373-82.

^{*1}Muller JE, Gunther SJ. Nifedipine therapy for Prinzmetal's angina. *Circulation* 1978; **57**: 137-9.

^{*2}Clark DA, Quint RA, Mitchell RL, Agnelli WW. Coronary artery spasm. Medical management, surgical denervation and autotransplantation. *J Thorac Cardiovasc Surg* 1977; **73**: 332-9.

Requests for reprints to Professor Attilio Maseri, Cardiovascular Research Unit, RPMS, Hammer-smith Hospital, Du Cane Road, London W12 0HS.